REMARKS

Claims 44-46 and 49-52 are pending in this application. The present rejections to the claims are respectfully traversed.

Information Disclosure Statement

Applicants thank the Examiner for considering the Information Disclosure Statement submitted.

Correction of Inventorship

The Examiner indicated that the inventorship in this application has been changed in the previous Office Action. Applicants note that they have yet to receive a corrected Filing Receipt. A corrected Filing Receipt is respectfully requested.

Rejections under 35 U.S.C. § 101 and 112, first paragraph

Claims 44-46 and 49-52 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by a credible, specific and substantial asserted utility or a well established utility.

Claims 44-46 and 49-52 stand rejected also under 35 U.S.C. § 112, first paragraph. Specifically since the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art would allegedly not know how to use the claimed invention.

Previously Applicants had provided Declarations under 37 C.F.R. § 132 of Audrey Goddard, Avi Ashkenazi and Paul Polakis in support of their position that the claimed invention has utility and is enabled.

The Patent Office indicates that the gene amplification assay does not establish a substantial utility for PRO269 polypeptides, to which this application is directed. The Patent Office agrees that the asserted utilities of cancer diagnostics and cancer therapeutics for the claimed proteins are credible and

specific. However, the Patent Office asserts that the utilities are not substantial. Specifically, the literature allegedly evidences that gene amplification does not reliably correlate with increased mRNA or protein expression. Therefore, further research would allegedly be required to determine if the disclosed results regarding a gene amplification event in tumors is also reflected at the mRNA and protein levels. The gene amplification data are preliminary with respect to whether or not the claimed protein can be used as a cancer diagnostic. Since the asserted utility that the claimed polypeptides can be used as cancer diagnostics is allegedly not in currently available form, the asserted utility is allegedly not substantial.

For the reasons outlined below, Applicants respectfully disagree. With respect to claims 44-46 and 49-52, Applicants submit that not only has the Patent Office not established a *prima facie* case for lack of utility and enablement, but that the PRO269 polypeptides possess a credible, specific and substantial asserted utility and are fully enabled.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has

asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Applicants have asserted utility for the PRO269 polypeptides, for example in the detection of lung cancer, which represents a specific, substantial and credible utility that entirely meets the utility standards set by the USPTO.

Arguments

It is well known that gene amplification occurs in most solid tumors and is generally associated with poor prognosis. As shown in Example 92 and Table 9 of the specification, PRO269 showed approximately 2-3 fold amplification in 8 primary lung tumors.

The Office Action indicates that "the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO269. There is no evidence regarding whether or not the PRO269 mRNA or polypeptide levels are also increased in these tumor samples. Since the instant claims are directed to PRO269 polypeptide, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased mRNA and polypeptide levels" (page 6 of Office Action).

Applicants submitted the Declaration by Audrey Goddard, Ph.D. which clearly establishes that the TaqMan realtime PCR method described in Example 92 has gained wide recognition for its versatility, sensitivity and accuracy and is in extensive use for the study of gene amplification. Dr. Goddard in her Declaration confirms that an at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e. non-tumor) is significant and useful. The Declaration further confirms that based on the gene amplification results set forth in Table 9, one of ordinary skill would find it credible that a 2 -fold increase in gene copy number (as seen with PRO269) would indicate that the gene is a diagnostic marker of human lung cancer.

Applicants further submitted the Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and a Director of the Molecular Oncology Department at Genentech, Inc., the assignee of the present application. In his Declaration, Dr. Ashkenazi states:

> "If gene amplification results in over-expression of the mRNA and corresponding gene product, then it identifies that gene product as a promising target for cancer therapy, for example by the therapeutic antibody approach."

Applicants previously submitted articles which show that generally, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (*Mol. and Cell. Proteomics*, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, Vol. 62, pages 6240-45) showed, using CGH analysis on cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, Vol. 99, pages 12963-12968, copy enclosed) who studied a series of primary human breast tumors and showed that "62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." (emphasis added) Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

The Office Action states Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of gene. It is not clear whether or not PRO269 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore the relevance of Orntoft et al. is allegedly not clear. Hyman et al. used the same CGH

approach in their research. Less than half of highly amplified genes showed mRNA overexpression (abstract). Therefore Hyman et al. also allegedly do not support utility. Pollack et al. also used CGH technology concentrating on large chromosome regions showing high amplification. Therefore Pollack et al. also allegedly do not support the asserted utility of the claimed invention.

In Ornoft et al., 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornoft et al. used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Ornoft et al found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (page 40). Ornoft et al. states "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (page 41, col. 1). Ornoft et al., also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Ornoft et al., states "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations...26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." Clearly Ornoft et al. support Applicants position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner indicates that Applicants have not indicated whether PRO269 is in a gene cluster region of a chromosome. Applicants fail to see how this is relevant to the analysis. Ornoft et al. did not limit their findings to only those regions of amplified gene clusters. Further, as discussed below, Hyman et al. and Pollack et al. did gene-by-gene analysis across all chromosomes.

The Office Action has mischaracterized the methods used by Hyman et al. and Pollack et al in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman et al., 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs were hybridized to the cDNA sequences. For expression analysis , RNA from tumor cell lines were hybridized on the same microarrays. The 13,824 arrayed

cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman et al. states that the cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome (page 6242, col. 2). Hyman et al. states that up to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (i.e., belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number. Therefore, the analysis performed by Hyman et al was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack et al., DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Parallel microarray measurements of mRNA levels revealed "the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells". (Abstract) "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)" (page 12966). Therefore, the analysis performed by Pollack et al. was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

With regard to the correlation between mRNA expression and protein levels, Applicants previously submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the

level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

The Office Action states that Dr. Polakis Declaration is insufficient to overcome the rejection since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels. Further, only Dr. Polakis' conclusions are provided in the Declaration. There is not evidentiary support to Dr. Polakis statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide.

Applicants submit that Dr. Polakis Declaration is presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Regarding, the Examiner's rejection of the Polakis Declaration "for not being supported by evidence of record", Applicants respectfully draw the Examiner's attention to the Utility Examination Guidelines , Part IIB, 66 Fed. Reg. 1098 (2001) which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered". The statement in question from an expert in the field (the Polakis declaration) which states: "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell.", would be considered reasonable and accurate by one skilled in the art. Therefore, barring evidence to the

contrary regarding the above statement in the Polakis declaration, this rejection is improper under the Utility guidelines.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO269 gene, that the PRO269 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO269 polypeptides and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

The Examiner cites Hu et al. for support that genes displaying a 5-fold change or less in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease.

Applicants disagree with the applicability of Hu et al. in this case. Applicants note that Hu et al. only studies the statistical analysis of micro-array data and not gene amplification data. Therefore, their findings would not be directly applicable to the gene amplification data. In addition, Applicants respectfully submit that the Hu et al. reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

First, the analysis by Hu et al. has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene

symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Secondly, Applicants submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules are overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusions based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al* admit that ., "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "[t]his may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

Applicants submit that even if gene amplification does not result in overexpression of the gene product (i.e. the protein) an analysis of the expression of the protein is useful in determining the course of treatment. Dr. Ashkenazi in his Declaration (previously submitted) stated:

"...even when amplification of a cancer market gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment."

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene product (the protein) is not over expressed. As indicated by Dr. Ashkenazi in his declaration. If a gene is amplified but the corresponding gene product is not over expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

In summary, Applicants respectfully submit that the Examiner has not shown a lack of correlation between gene amplification data and the biological significance of cancer genes.

On the other hand, Applicants have clearly demonstrated a credible, specific and substantial asserted utility for the PRO269 polypeptide and for the antibody that specifically binds to PRO269. Further, based on this utility and the disclosure in the specification, one skilled in the art would know how to use the claimed polypeptides at the time of filing. Withdrawal of the rejections under 35 U.S.C. § 101 and 35 U.S.C. § 1112, first paragraph is respectfully requested.

CONCLUSION

It is submitted that the present application is in form for allowance, and such action is respectfully requested.

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. 08-1641 (Docket No.39780-1618 P2C33).

Respectfully submitted,

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By: _____
Leslie A. Mooi (Reg. No. 37,047)

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer Number: 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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(39780.1618)